Evaluate Vantage

November 26, 2018

Combination trial could be start of second act for Amgen’s Imlygic

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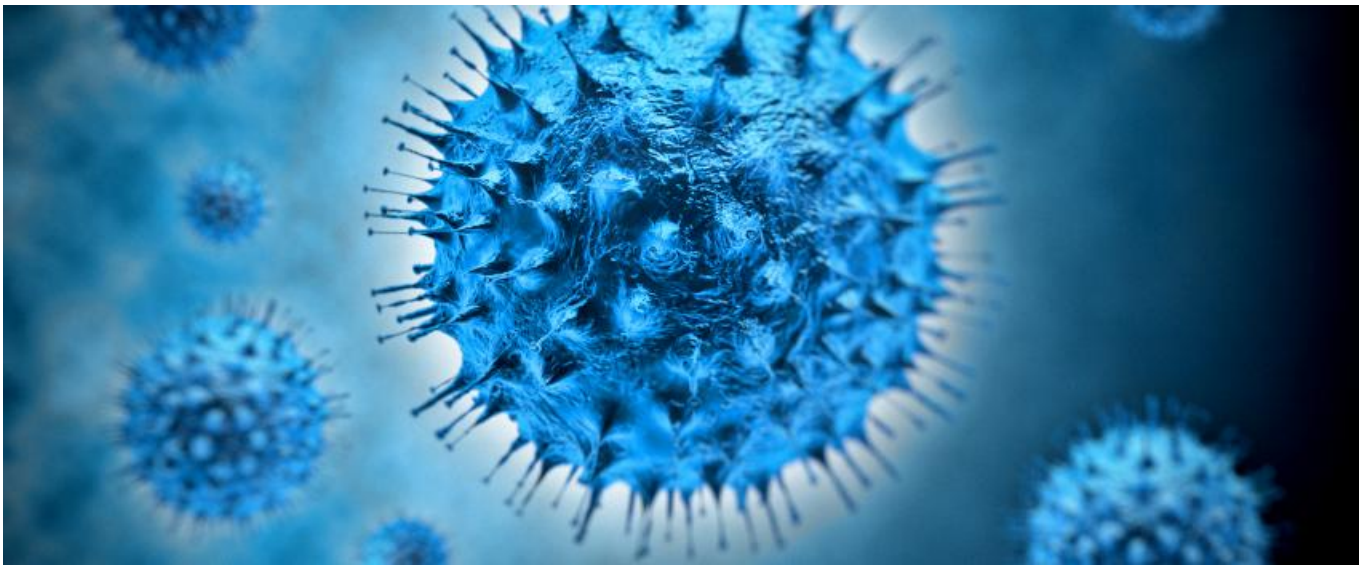

Masterkey-265 will test the sector’s renewed interest in oncolytic viruses as a way of turning “cold" tumours "hot”.

Imlygic was a scientific achievement that disappointed commercially. The first oncolytic virus had the misfortune of being launched just as the anti-PD-1 antibodies Opdivo and Keytruda were transforming the treatment of melanoma, and partly as a result has fallen well short of forecasts.

The Amgen product now has a chance to redeem itself, with results due in December from the Keytruda combination trial Masterkey-265 in first-line disease. Melanoma is one of the few settings in which Bristol-Myers Squibb’s Opdivo has outmanoeuvred Merck & Co’s Keytruda, so positive results from this study could help both Merck and Amgen.

Less toxic

The trial, also known as Keynote-034, pits the Imlygic-Keytruda combination against Keytruda alone in 713 patients, hoping to show a benefit on progression-free and overall survival. The benchmark against which the combination will be judged will be the 11.5 months of PFS achieved by a combination of Opdivo and Yervoy in the Checkmate-067 trial, in which the Bristol combination reduced the risk of progression by 58%.

Study	Setting	Treatment	Trial ID
Masterkey-265/Keynote-034	Melanoma	Keytruda +/- Imlygic	NCT02263508

Alone, Keytruda can achieve 5.5 months of PFS on average, equating to a 42% reduction in risk of progression versus Yervoy monotherapy. Imlygic gained approval on the basis of a durable response rate of 16.3%, compared with 2.1% in a comparator arm treated with GM-CSF. The overall survival for patients treated with Imlygic was 22.9 months, statistically no better than the 19 months in the GM-CSF arm.

So far, the Merck-Amgen combo has not met the Opdivo-Yervoy benchmark: phase Ib results showed a confirmed overall response rate of 48%, similar to the 50% ORR reported by Opdivo plus Yervoy in Checkmate-067.

But there is an expectation that Keytruda-Imlygic could amount to a less toxic combination, meaning that it

probably only needs to show similar survival benefit. In Checkmate-067, 73% of patients on Opdivo-Yervoy experienced severe adverse events, and 43% discontinued treatment because of these.

By comparison, Keytruda's discontinuation rate was 9% in its melanoma trial Keynote-006, and Imlygic's main side effect is low-grade flu-like symptoms, and no grade 3 toxicities occurred in more than 3% of patients tested.

On dosing, patients taking Opdivo-Yervoy undergo consecutive infusions of the two immunotherapies. By comparison, patients on the Keytruda-Imlygic regimen would have to undergo an infusion of the immunotherapy accompanied by intralesional injections.

If the two combos seem balanced on efficacy it seems a good bet that physicians will favour the one that patients are more likely to tolerate. But whether the Opdivo-Yervoy toxicity is enough to cause patients to prefer the fortnightly Imlygic injections – which require practitioners to move the needle around each lesion to maximise the dispersion – will only become clear should the Merck-Amgen combination get approval.

Betting on viruses

Positive data for a PD-1/oncolytic virus combination could be just the start of a new phase of Merck's expansion of its Keytruda empire. The big pharma group has committed further to oncolytic viruses with the acquisition of Australian group Viralytics, which brought along another project, Cavatak.

Merck had tested intravenous combinations of Keytruda and Cavatak, which would take treatment with oncolytic viruses beyond the accessible tumours that Imlygic can now reach. Merck published data from a phase Ib trial at Esmo indicating an overall response rate of 23% in non-small cell lung cancer and 33% in bladder cancer.

There has been a flurry of recent oncolytic virus deals, in part built around the idea that this treatment approach can render non-immunogenic tumours susceptible to treatment with immunotherapies (*Oncolytics prepares to tap US investors, September 21, 2018*). Data from the Imlygic-Keytruda trial will be an early indicator of whether this is money well spent.